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Introduction: High dose therapy followed by autologous hematopoietic stem cell transplantation (ASCT) has an established role in the treatment of patients with multiple myeloma (MM). The CR rate, an indicator for progression-free and overall survival (PFS; OS) observed after the most commonly used conditioning regimen Mel200 (Melphalan 200mg/m^2) is between 10-35%. The objective of our trial is to assess whether conditioning with a combination of PK-directed Busulfan (Bu), Mel and Bortezomib (Btz) is safe and can improve CR rates in patients with MM.

Methods: Patients aged 18-72 with MM, who had received less than one year of prior myeloma-directed therapy and were eligible for ASCT were assigned to receive PK-directed i.v. Bu, i.v. Mel and i.v. Btz as per Fig. 1. Subsequent consolidative or maintenance therapy was left to investigator's choice. Primary outcome was CR rate assessed on D +100 post ASCT as per IMWG criteria. Secondary outcomes are overall response rate (ORR), toxicities, PFS and OS. The trial is registered at clinicaltrials.gov (NCT01605032).

Results: To date, 18 patients have been treated (median age 61 (range 44-70), 61% male, 17% with ISS stage 3; median number of prior regimens 1 (range 1-3); prior bortezomib 94%). For the 12 evaluable patients the median days to ANC >/=0.5 x 10^9/L and platelet count >/=30 x 10^9/L were 11 (range 10-13) and 17 (11-29), respectively. The most common non-hematological toxicities (100%) were alopecia, oral mucositis (62% G3), dysphagia (85% G3), as well as electrolyte abnormalities (62% ≥G3). Other common toxicities were nausea (92%, all G1/2), diarrhea (84% G1/2, 15% G3), while 84% of patients developed fully reversible transaminitis (15% G3). Less common G3 toxicities included delirium (8%), colitis (8%), skin infection (15%; zoster & skin abscess, 1 each), other infections (31%), and engraftment syndrome (8%). No patient developed sinusoidal obstruction syndrome of the liver. Response assessment was available for 11 patients: 1 achieved a stringent CR (9.1%), 5 VGPR (45.5%), and 5 PR (45.5%), resulting in a 100% ORR. After a median follow up of 5.2 months (range 1-18) all patients are alive and no patient has relapsed. The trial is ongoing.

Conclusion: PK directed i.v. Bu in combination with Mel and Btz (BuMelBtz) is an effective and safe conditioning regimen for patients with MM. Further evaluation is warranted.

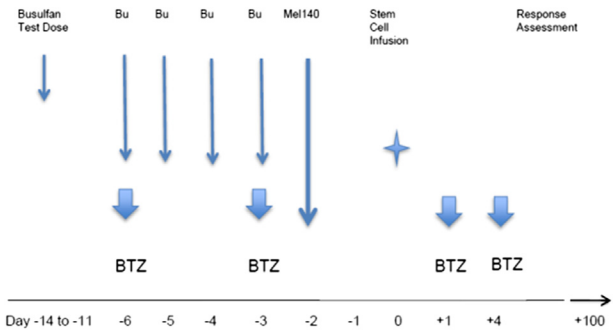

Fig. 1. Treatment Schema
Following a Busulfan (Bu) test dose (0.8mg/kg) prior to the first treatment dose, intravenous (i.v.) Bu is given 4 times daily as 3-hour infusion from day (D) -6 to -3 to target a total AUC of 20,000 uMxmin (PK-directed Busulan); i.v. Melphalan (Mel; 140mg/m2) is given on D-2, and i.v. Bortezomib (BTZ; 1.4mg/m2) on D-6, -4, +1 and +4.

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Chemosensitivity to Induction or High Dose Therapy, Pre/Post Transplant PET Negativity and Absence of Minimal Residual Disease within Mobilized Stem Cell Graft Predict Long Term Disease Free Survival in Multiple Myeloma

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Despite the improvements in response rates in multiple myeloma during the last decade, relapses still remain as a problem. Aim of this study was to evaluate the factors associated with response and the length of progression free survival (PFS) following autologous hematopoietic cell transplantation (ASCT). Out of 113 consecutive patients with newly diagnosed MM, 43 % and 19% achieved Post-ASCT complete remission (CR) or very good partial remission (VGPR) respectively. Post-ASCT response status was significantly associated with female sex, light chain myeloma, β-2 microglobulin (≤3.5mg/L) and pre-ASCT response status. Multiparameter flow cytometry detected abnormal plasma cells (APC) in the harvests of 9.7% of patients. Higher proportion of patients who had contaminated harvests were at <VGPR status during mobilization compared to patients who did not have contamination (73% vs 53%; p=.088). Presence of APC in the harvests compared to those lacking APC was significantly associated with progression at 12 months after ASCT (75% vs 36%; p=.039). The median PFS was 13 (2-45) months after a median follow-up of 33 (7-148) months.

Table
Factors Affecting the Post-transplant Progression Free Survival

	PFS (months) mean ±SD	95% CI	*P*
Sex	26.1 ± 2.6	21.0-31.2	.135
Female	20.3 ± 2.2	16.0-24.5	
Male			
Subtype	30.6 ± 3.0	24.7-36.5	.008
Light chain	20.3 ± 1.9	16.5-24.1	
Others			
International Staging System	27.2 ± 2.8	21.7-32.7	.047
ISS1	24.2 ± 2.9	18.6-29.9	
ISS2	15.9 ± 2.7	10.7-21.1	
ISS3			
Cytogenetics	24.0 ± 3.1	18.1-30.0	.101
del13q negative	14.5 ± 2.5	9.4-19.5	
del13q positive			
β 2 microglobulin, mg/L	25.7 ± 2.7	20.5-30.9	.230
≤3.5	20.9 ± 2.2	16.5-25.2	
>3.5			
Post-transplant PET	30.1 ± 3.2	23.9-36.3	.008
Negative	17.8 ± 2.6	12.7-22.8	
Positive			
APC in harvests	24.0 ± 1.9	20.4-27.7	.206
Absent	14.4 ± 3.3	8.0-20.8	
Present			
Pre-transplant response	14.8 ± 3.8	7.3-22.2	.021
<PR	19.9 ± 2.5	15.0-24.8	
PR	28.2 ± 4.3	19.8-36.7	
VGPR	28.4 ± 2.8	22.8-33.9	
CR			
Post-transplant response	3.2 ± 1.2	0.85-5.55	.001
<PR	17.1 ± 2.8	11.6-22.6	
PR	30.9 ± 3.7	23.7-38.0	
VGPR	26.9 ± 1.8	19.8-26.7	
CR			

Myeloma subtype, ISS, post-ASCT response and PET activity were significantly associated with PFS. Post-ASCT PET(-) CR had significantly longer PFS than patients with PET(+) CR (31.4 ± 9.9 vs 18.4 ± 3.5 months; p=.029). In conclusion, having an ISS-3 stage myeloma, pre and post-ASCT response <VGPR had negative impact on PFS. Contamination of PBSC harvests with APC was associated with shorter PFS. Our results also demonstrate the importance of achieving PET negativity after transplantation. Thus, not only an immunological CR but also PET(-) CR should be achieved for long term PFS.

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Incidence and Risk Factors for the Development of Idiopathic Pneumonitis Syndrome (IPS) after Autologous Hematopoietic Cell Transplantation (AutoHCT) for Patients with Lymphoma

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Introduction: High-dose therapy with AutoHCT is a standard component of therapy for many patients with Hodgkin (HL) and non-Hodgkin lymphoma (NHL). IPS is a known toxicity of AutoHCT which can cause significant morbidity and mortality. The most common agent associated with IPS has traditionally been high-dose BCNU (carmustine). Data on incidence of IPS in recent era and its relation with conditioning regimens are scarce.

Methods and Patients: Using the Center for International Bone Marrow Transplant Registry (CIBMTR), we studied 4,573 patients with lymphoma who underwent AutoHCT from 1995-2008 using the following conditioning regimens: BEAM (n=1730), CBV^{low} (n=1249), CBV^{high} (n=604), BuCy (n=789), and CyTBI (n=545). We investigated the reported incidence of and explored clinical risk factors for its development, including the dose of BCNU and its impact on outcome (above vs. below 375 mg/m^2 in CBV regimens). We then analyzed the impact of IPS on outcomes including transplant-related mortality (TRM), progression-free survival (PFS), and overall survival (OS). Use of different regimens was as follows:

Results: The incidence of IPS by 1 year after AutoHCT was: BEAM (3%), CBV^{low} (3%, HR 1.07 [0.72, 1.60], p=0.742), CBV^{high} (6%, HR 1.88 [1.24, 2.83], p=0.003), BuCy (4%, HR 1.25 [0.82, 1.92], p=.30), and CyTBI (5%, HR 2.03 [1.30, 3.19], p=.002). Multivariate analysis showed the following risk factors for developing IPS: 1) HL (HR 2.33, [1.68, 3.24], p < .001), 2) female gender (HR 1.39 [1.05, 1.82], p=.019), 3) chemotherapy-resistant disease at time of AutoHCT (HR 1.9 [1.29, 2.79], p=.001), and age ≥ 55 (HR 1.54, [1.13, 2.09], p=.006). In the entire cohort, patients who developed IPS had a significantly higher rate of TRM (HR 4.02, [3.09, 5.24], p < .001), shorter PFS (HR 1.82, [1.51, 2.20], p < .001), and shorter OS (HR 2.46, [2.06, 2.94], p < .001).

Conclusion: IPS remains an important toxicity after AutoHCT for patients with lymphoma and adversely effects overall outcomes. Risk factors include higher doses of BCNU, TBI, female gender, older age, chemotherapy resistant disease and a diagnosis of HL. Investigation into strategies for the prevention of IPS after ASCT is warranted.

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Suboptimal Long Term Engraftment Does Not Negatively Impact Overall Survival after Autologous Peripheral Blood Stem Cell Transplant

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The importance of optimal long term engraftment after autologous stem cell transplantation is uncertain. We conducted a retrospective analysis of long term engraftment in patients who underwent autologous peripheral blood stem cell transplant for non-Hodgkin lymphoma, Hodgkin lymphoma or multiple myeloma. Patients who relapsed or died prior to assessment of long term engraftment at 1 year were excluded. Optimal engraftment was defined by NCI CTCAE grade 1 criteria for cytopenias (ANC ≥ 1500/ml, platelets ≥ 75000/ml, hemoglobin ≥ 10g/dL). 225 patients were identified with engraftment data at 1 year (92 NHL, 62 HL, 71 MM). The median follow-up was 5.0 years for all patients (5.5 for living patients).

88% of patients achieved optimal engraftment at 1 year. The median cell dose was 4.7 x10-6 CD34+ cells/kg, and our institutional minimum cell dose is 2 x10-6 CD34+ cells/ kg. CD34 cell dose ≥ 3 x10-6 CD34+ cells/kg and age < 60 were predictive for optimal long term engraftment. Disease type, gender, number of prior therapies and prior radiation therapy were not predictive of achieving long term engraftment. By landmark analysis at 1 year, optimal engraftment was not predictive for progression free survival or overall survival in all patients, although there was a trend for worse outcome with poor engraftment in HL and NHL.

Incomplete long term engraftment after autologous transplant is relatively rare with the most important predictors identified as CD34 cell dose and age. For those patients who survive one year, PFS and OS are not diminished afterward.

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25-Hydroxyvitamin D Concentrations and Overall Survival in Autologous Hematopoietic Stem Cell Subjects

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